REMARKS

Restriction Requirement:

Applicants acknowledge with appreciation the Examiner's withdrawal of the restriction between Groups II and III.

Drawings:

Applicants will defer submission of formal drawings meeting the requirements of 37 CFR 1.84 prior to, or on the date of, payment of the issue fee.

New Claims:

Applicants have added new Claims 22-29, to more particularly describe the present invention. Support for these claims is found in the original claims and in the specification, page 16, line 24 to page 19, line 5; page 24, line 3 to page 25, line 24; page 26, lines 12-16.

Rejection of Claims 1-9 and 13 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-9 and 13 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite for failing to particularly point out and distinctly claim the present invention. Specifically, the Examiner first objects to the use of the term "preferentially" in Claim 1. The Examiner asserts that this term is a relative term which renders the claim indefinite.

Applicants traverse the Examiner's contention that the term "preferentially" renders the claim indefinite. First, Applicants note that the term "preferential" has a clear meaning when used to reference ligands binding to and acting through multiple receptors. This is well known to those of skill in the art. In the case of many mammalian receptors, analogs with higher affinity to one or another receptor are well known. Implicit in the concept of "preferential" is a standard against which relative binding affinity and activity of various analogs is related. For example, in the present case, one can compare the binding of a given compound from one receptor to another or the activity induced by such a compound from one receptor to another, and thereby readily determine on which receptor the given compound preferentially acts. In addition, or alternatively, one could readily compare the binding or activity of a given compound to the binding or activity of the natural ligand

standard, MSH. Applicants note that the claims already clearly recite that a compound that induces greater activity of the peripheral receptors (e.g., MC2-R or MC5-R) as compared to the central receptor, MC4-R, is identified as a compound that regulates body weight by preferentially targeting the peripheral receptors. Applicants submit that this term is not indefinite, particularly when the claim explicitly recites how one is to determine whether a ligand preferentially acts on a peripheral receptor as compared to a central receptor.

Second, the Examiner objects to the use of the abbreviation "POMC" in Claims 6-9 and 13 as being indefinite. Applicants have amended these claims to spell out the abbreviation at its first use.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-9 and 13 under 35 U.S.C. § 112, second paragraph.

Objection to the Specification and Rejection of Claims 1, 6, 15 and 17 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 6, 15 and 17 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner acknowledges that the specification is enabling for the identification of compounds that regulate the melanocortin 2-receptor (MC2-R) and MC5-R, but contends that the specification does not enable the identification of compounds that regulate body weight. The Examiner asserts that the disclosure does not teach how compounds identified by the method can be used to regulate body weight with a reasonable expectation of success that they would have the desired effect.

Applicants traverse the Examiner's contention that the specification does not enable the identification of compounds that regulate body weight. The present inventors have shown, through working examples provided in the specification, that administration of a melanocortin agonist to an animal that is obese reduces obesity in the animal. Although prior to the present invention, several lines of investigations placed proopiomelanocortin (POMC) and the peptides derived from it at a pivotal position in the *central* pathways for energy homeostasis, the present inventors were the first to appreciate and demonstrate the role of melanocortin agonists (including the natural agonist, MSH), in the regulation of body weight via *peripheral* pathways of energy homeostasis. More

specifically, Examples 2-5 of the specification clearly shows that administration of an MSH agonist is effective to decrease the body weight of obese mice as compared to in the absence of the compound. Referring to Example 2, since the genetically matched control mice were maintained on the same diet and activity level as the experimental mice, the effect was clearly substantially due to the peripheral administration of the MSH agonist and not to some other natural effect such as small degrees of weight gain or loss as a result of eating or exercise. Examples 3-5 provide additional evidence that reduction in body weight and/or a decrease in the rate of weight gain (e.g., see Example 5) are significantly attributable to the administration of the MSH analog. Moreover, the present inventors have now published results demonstrating that the mice have increased lipolysis following MSH treatment, further indicating the peripheral activity of MSH agonists on peripheral mechanisms of homeostasis (Forbes et al., 2001, *Proc. Natl. Acad. Sci. USA* **98**(7):4233-4237; see in particular page 4234-4235 and Figure 5).

Since MSH agonists bind to the melanocortin receptors, peripheral melanocortin receptors are desirable targets for an assay to identify additional compounds that regulate such receptors. In view of the present inventors discovery that the basis for weight loss in the mouse model for obesity is largely a peripheral mechanism, the present claims are directed to the identification of compounds that preferentially bind to and activate the *peripheral* melanocortin receptors as compared to the central receptor, MC4-R. Using the guidance provided in the specification and in view of the level of skill in the art, all of the steps of the method can be performed by the skilled artisan, as the Examiner appears to acknowledge. The present inventors have already demonstrated that known compounds (e.g., known melanocortin agonists) that bind to the peripheral receptors can regulate body weight and the peripheral mechanisms of energy homeostasis. Therefore, it is submitted that the present method is fully enabled.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 6, 15 and 17 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claim 19 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claim 19 under 35 U.S.C. § 112, first paragraph, contending that the specification does not enable the identification of compounds

that regulate the peripheral pathways of energy homeostasis. The Examiner asserts that there is no guidance provided in the specification as to how one of ordinary skill in the art would correlate the compounds identified that regulate MC2-R or MC5-R with regulating the peripheral pathways of energy homeostasis.

Applicants traverse the Examiner's contention that there is no guidance provided in the specification as to how one of ordinary skill in the art would correlate the compounds identified that regulate MC2-R or MC5-R with regulating the peripheral pathways of energy homeostasis. Applicants refer to the discussion above and again submit that the specification does in fact demonstrate a basis for the regulation of body weight and the peripheral pathways of energy homeostasis using melanocortins, that these compounds bind to the recited receptors (e.g., to peripheral melanocortin receptors), and that the identification of other compounds that bind to the receptors (i.e., by practicing the claimed method) would reasonably be expected to act in the same way. If one identifies a compound that regulates the activity peripheral melanocortin receptors, one would have a reasonable expectation, based on the *in vivo* data provided in the specification and additional experiments performed subsequent to the invention (See Forbes et al., *ibid.*), that such compounds will be useful for regulation of peripheral pathways of energy homeostasis.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 19 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-9 and 15-21 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-9 and 15-21 under 35 U.S.C. § 103, contending that these claims are not patentable over Lee et al. in view of Boston et al. Specifically, the Examiner contends that Lee et al. teach the use of cellular and non-cellular assays of compounds that interact with MC4-R. The examiner admits that Lee et al. do not expressly disclose the identification of compounds that regulate MC2-R or MC5-R in order to regulate peripheral pathways of energy homeostasis or the identification of compounds using isolated adipocytes. The Examiner cites Boston et al. as allegedly teaching the expression of MC2-R and MC5-R in the peripheral tissues and that these receptors are modulated by many melanocortin peptides in adipocytes. Therefore, the Examiner asserts that it would have been obvious to modify the methods of Lee et al. to identify

compounds that regulate the MC2-R and MC5-R described in Boston et al. The Examiner contends that motivation is provided by Boston et al. in that this reference allegedly teaches that these receptors may be involved in the regulation of fat stores in adipose tissue. The Examiner therefore asserts that the claimed invention is *prima facie* obvious in view of the combination of references.

Applicants traverse the rejection of Claims 1-9 and 15-21 under 35 U.S.C. § 103. First, with regard to Lee et al., as the Examiner acknowledges, this patent is directed exclusively to the identification of compounds that bind to melanocortin 4-receptor (MC4-R), which is a *central nervous system receptor*. MC4-R is not expressed in the peripheral tissues. The present invention is predicated on the discovery by the present inventors that *peripheral* administration of melanocortin agonists (e.g., which bind to peripheral melanocortin receptors) can regulate body weight by regulating peripheral mechanisms of energy homeostasis. As emphasized in the specification, prior to the present invention, the central line of investigation of body weight regulation, in which Lee et al. can be included, pointed to the *central* melanocortin receptors, and particularly, MC4-R as pivotal. Indeed, the patent to Lee et al. is based on the conclusion that regulation of MC4-R is key to regulation of body weight. It was not until the present invention that it was demonstrated that peripheral activity of the melanocortins can regulate body weight. Indeed, the present claims are directed to the identification of compounds that are less active on the MC4-R than on the peripheral receptors, which is the opposite of what Lee et al. is teaching. Therefore, not only do Lee et al. fail to teach the present invention, it can readily be argued that Lee et al. *teach away* from the present invention and certainly that Lee et al. provide no motivation to the skilled artisan to make the combination as the Examiner has done.

Boston et al., even in combination with Lee et al., do not make up for the deficiencies of Lee et al. and emphasize the clear teaching away from the present invention. First, it is noted that the *in vitro* experiments shown by Boston et al. showed lipolytic activity of MSH in rabbit adipocytes, but relatively little stimulation of lipolysis in rat cells. Therefore, it is submitted that at best, one might conclude that the rabbit adipocyte is an anomaly. Second, although Boston et al. show the presence of MC2-R and MC5-R in adipose tissue, they state that the physiological relevance of MC5-R in the adipocyte is unclear and only speculate that the MC2-R may stimulate lipolysis during times of high stress in response to ACTH (see Boston et al., Discussion). Boston et al. do not

conclude that regulation of the peripheral melanocortin receptors should be targeted for regulation of body weight, and they fail to conclude that these receptors may be used to regulate energy homeostasis. Indeed, referencing the agouti mouse model of obesity, Boston et al. conclude that the absence of either the MC1 or MC4 receptors in the adipocyte "make the adipocyte a less likely target of agouti-mediated obesity" and emphasize the belief that the MC4 is the best target for regulation of feeding behavior and metabolism (see page 2048, col. 2, first and second full paragraph). This conclusion again underscores the common theory prior to the present invention that the MC4 receptor is pivotal in weight regulation, which would lead one to believe that regulation of melanocortin receptors expressed on the adipocyte may not be important for weight regulation.

Therefore, it is submitted that one of skill in the art would view the combination of Lee et al. and Boston et al. as a teaching to target the *MC4-R* for the identification of compounds that regulate body weight, which is a teaching away from the present invention. The combination fails to provide a teaching or suggestion to turn away from the MC4-R and to focus on the peripheral melanocortin receptors. Neither of Boston et al. or Lee et al. recognize the role of MSH agonists in the peripheral regulation of body weight and therefore, the combination can not teach or suggest to one of skill in the art to identify compounds that have such a role.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-9 and 15-21 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the concerns raised by the Examiner in the July 5 Office Action. The Examiner is encouraged to contact the below-named agent with any questions or concerns regarding Applicants' position.

Respectfully submitted,

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Marked-up Version Showing Amendments

Claims 10-14 have been canceled.

Claims 6 and 19 have been amended as shown below.

Claims 1-5, 7-9, 15-18 and 20-21 have not been changed.

Claims 22-29 have been added.

6. (Once Amended) A method for identifying compounds that increase body weight by regulating peripheral pathways of energy homeostasis, comprising:

a. contacting a cell which expresses a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R) with a proopiomelanocortin (POMC) compound which binds to and activates said melanocortin receptor in the presence and absence of a putative regulatory compound;

b. detecting whether said putative regulatory compound inhibits said melanocortin receptor activity;

wherein putative regulatory compounds that inhibit said melanocortin receptor activity are identified as compounds that increase body weight by regulating peripheral pathways of energy homeostasis.

19. (Once Amended) A method for identifying compounds that regulate peripheral pathways of energy homeostasis, comprising:

(a) contacting a putative regulatory compound with an isolated adipocyte; and,

(b) detecting putative regulatory compounds that bind to a melanocortin [repector] receptor on said adipocyte, wherein putative regulatory compounds that bind to melanocortin receptors on said adipocytes are identified as compounds that regulate body weight by regulating peripheral pathways of energy homeostasis.